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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/731,375	12/08/2003	Philip J. Barr	368292001700	4368

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HELLER EHRMAN LLP
275 MIDDLEFIELD ROAD
MENLO PARK, CA 94025-3506

EXAMINER	
KIM, JENNIFER M	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 03/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/731,375	BARR ET AL.	
	Examiner	Art Unit	
	Jennifer Kim	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5,8,11 and 13-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5,8,11 and 13-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicants' submission filed on December 6, 2005 has been entered.

Action Summary

The rejection of claims 5, 8, 11 and 13-17 under 35 U.S.C. 103(a) as being unpatentable over Avidano et al. (Head and Neck Surgery, Oct., 1998) in view of Grote et al. (U.S.Patent No. 6,670,327B1) of record and further in view of Brake et al. (U.S.Patent No. 4,752,576) are being maintained for the reasons stated in the previous Office Action. This rejection is modified in this Office Action to include newly added claims 18-21.

Applicants' amendment necessitated the additional rejection and objections presented in this Office action.

Claim Objections

Claim 19 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicants are required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The claim 19 depend from claim 18 and it does not constitute a further limiting claim 18 because the amount ranges of the active agents are broader than the amounts set forth in claim 18.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 20 and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

With regard to claim 20 recites the limitation "wherein hearing loss" in line 1. There is insufficient antecedent basis for this limitation in the claim.

With regard to claim 21 recites the limitation "wherein an otic inflammatory response" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

Claims 5, 8, 11 and 13-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Avidano et al. (Head and Neck Surgery, Oct., 1998) in view of Grote et al. (U.S.Patent No. 6,670,327B1) of record and further in view of Brake et al. (U.S.Patent No. 4,752,576).

Avidano et al. teach otorrhea samples were collected from patients with otitis media and a perforated tympanic membrane and the samples were treated with ilomostat plus alpha1-antitrypsin in *vitro*. (abstract). A statistically significant ($p<0.05$) decrease in protease activity was observed. (see Fig. 1, page 348).

Avidano et al. do not teach the actual *vivo* treatment of an individual having otitis media with a perforated tympanic membrane; causes of otorrhea and tympanic membrane perforations due to post-tympanostomy and tympanostomy; effective amount; further comprising steroid; the source of the alpha-1 antitrypsin is yeast-expressed rAAT and the result of the treatment set forth in claims 20 and 21.

Grote et al. teach the use of corticosteroids for the treatment of otitis media (column 2, lines 2, lines 34-45). Grote further teaches a treatment of otitis media with or without tympanostomy. (column 6, lines 50-55). Grote et al. teach that conditions such as tympanic membrane perforation are complications associated with otitis media. (column 6, lines 20-35).

Brake et al. teach a method for producing alpha1-antitrypsin (AAT) by recombinant methods from yeast. This method provides high level production of the protein. (abstract, column 1, lines 59-68, column 2, lines 7-15).

It would have been obvious to one of ordinary skill in the art to treat patients with otitis media with a perforated tympanic membrane with a combination of alpha1-antitrypsin and ilomastat for the treatment of any otitis media patients with otorrhea resulting form tympanic membrane perforation irrespective of the cause of how the perforations are caused by since the combination statistically decrease protease activity which is beneficial in treatment of otitis media. The motivations to employ this combination comes from Avidano et al's teaching that this combination is more effective in treatment regimen than either ilomastat or alpha1-antitrypsin alone.

To employ corticosteroid to Avidano et al's regimen to treat a patient with otitis media and a perforated tympanic membrane would have been obvious because all the components are well known individually for treating otitis media and corticosteroids are well known by Grote et al. for the treatment of otitis media. The motivation for combining the components flows from their individually known common utility (see In re Kerkhoven, 205 USPQ 1069(CCPPA 1980)).

It would have been obvious to one of ordinary skill in the art to employ the recombinant AAT obtained by yeast –expressed rAAT because Brake et al. teach the method of producing alpha1-antitrypsin (ATT) by recombinant methods in yeast provides high level production of the protein. One would have been motivated to employ yeast-expressed rAAT in Avidano et al's combination because the method of

producing the alpha1-antitrypsin by yeast method provided high level of production and is well known by Brake et al.

The amounts of active agents to be used all deemed obvious because once the usefulness of the combination is known to treat a condition, it is within the skill of the artisan to determine the optimum amounts. It has been held that it is within the skill in the art to select optimal parameters, such as amounts of ingredients, in a composition in order to achieve a beneficial effect. See *In re Boesch*, 205 USPQ 215 (CCPA 1980). The route of administration including topical administration is obvious because it is a routine route of administration practiced by skilled in the art to treat otitis media.

The results of decrease in otic inflammatory response is reduces in the treated individual relative to an untreated individual is obvious because Avidano et al's vitro data shows statistically significant ($p<0.05$) decrease in protease activity was observed in otorrhea sample collected from the patient suffering from otitis media. One of ordinary skill in the art would allow in *vitro* data shown by Avidano et al. as a surrogate for in *vivo* behavior.

Thus, the claims fail to patentably distinguish over the state of the art as represented by the cited references.

None of the claims are allowed.

Response to Arguments

Applicants' arguments filed December 6, 2005 have been fully considered but they are not persuasive. Applicants argue that the references fail to teach or suggest all of the claim elements because none of the references, either alone or when combined, teach or suggest a method that includes delivering to any individual or individual having otitis media and perforated tympanic membrane, an effective nonototoxic amount of recombinant ATT to the middle ear by topical application to the external auditory canal. This is not persuasive because the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. In this case, Avidano et al. teach the actual protease activity inhibition with a sample of otorrhea from patients actually suffering from otitis media and a perforated tympanic membrane and Avidano et al. teach that the combination comprising both Ilomostat and a-AAT resulted in a statistically significant decrease in the protease activity. This *vitro* data is a motivation that there is a reasonable expectation of success in *vivo* comprising the treatment of the actual of the sampled otorrhea patient suffering from otitis media and a perforated tympanic membrane patients disclosed by Avidano et al. The *vivo* treatment by employment of such combination taught by Avidano et al. is next logical step from the

significant decreasing result found by Avidano et al. Furthermore, no unobviousness is seen in the specific amounts claimed and administration of nontoxic amounts of medicinal composition to a patient because once the usefulness of a compound is known to treat a condition, it is within the skill of the artisan to determine the optimum amounts and nontoxic amount to deliver sufficient amounts required to treat a patient without any toxicity. Thus, the claims fail to patentably distinguish over the state of the art as represented by the cited references.

None of the claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Kim whose telephone number is 571-272-0628. The examiner can normally be reached on Monday through Friday 6:30 am to 3 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sreenivasan Padmanabhan
Supervisory Examiner
Art Unit 1617

Jmk
February 22, 2006